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VALUE IN HEALTH

Evaluating Interventions to Improve Antiretroviral Adherence: How Much of an Effect Is Required for Favorable Value?

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ABSTRACT

Objective: Uncertainty about the value of antiretroviral therapy (ARV) adherence interventions may be a barrier to implementation and evaluation. Our objective is to estimate the minimum effectiveness required for ARV adherence interventions to deliver acceptable value.

Methods: We used a validated HIV computer simulation to estimate the impact of ARV adherence interventions on incremental costs and life expectancy. Across a wide range of intervention costs ($1000–10,000, one time or per year), we estimated the smallest effect size compatible with acceptable value (incremental cost-effective ratio ≤$100,000 per life-year). Effect sizes were measured using relative risk (RR) and absolute risk reduction (ARR), and these metrics were applied to nonadherence and nonadherence risk factors. Costs were estimated from a societal perspective ($2003) discounted at 3%.

Results: To give acceptable value, a one-time $1000 intervention must reduce ARV nonadherence by RR ≤ 0.82 (ARR ≥ 0.04) for moderately nonadherent patients (20% of ARV doses missed) and RR ≤ 0.90 (ARR ≥ 0.05) for severely nonadherent patients (50% of ARV doses missed). A one-time $5000 intervention has an unacceptable value regardless of effect size for moderately nonadherent patients, and must reduce ARV nonadherence by RR ≤ 0.31 (ARR ≥ 0.69) for severely nonadherent patients. Interventions aimed at behavioral risk factors (e.g., unhealthy alcohol use) may confer acceptable value (e.g., if ≤$2000 and effect RR ≤ 0.71 [ARR ≥ 0.29]).

Conclusions: ARV adherence interventions with plausible effect sizes may offer favorable value if they cost <$5000 one time or per year. ARV adherence interventions with a favorable value should become more integral components of HIV care.

Keywords: adherence, AIDS, cost-effectiveness analysis, health services.

Introduction

Nonadherence with antiretroviral therapy (ARV) remains prevalent even though newer regimens have fewer side effects and lower pill burdens. Pharmacy refill records from a national health system suggest at least 37% of doses of all regimens are not taken as directed, and at least 33% of doses of efavirenz-based regimens are not taken as directed, even though they are noted for their tolerability [1]. At the same time, ARV nonadherence is a major cause of preventable morbidity and mortality among HIV-infected persons. Failing to suppress viral replication leads to higher rates of AIDS-defining events and deaths, and in the long term may induce drug-resistant viral strains. Indeed, observed levels of nonadherence would be expected to shorten life expectancy by as much as 3.9 to 7.0 years [2] or 2.9 to 5.9 quality-adjusted life-years [3].

Because improving ARV adherence has a great potential to lower morbidity and mortality in HIV-infected persons, it is important to evaluate interventions that aim to improve adherence. Adherence interventions (e.g., directly observed therapy), however, may be expensive, and value is becoming more important as an evaluation criterion. A formidable barrier to evaluating nonadherence interventions is the practicality of implementing an effective intervention because of its costs. In other words, an intervention must demonstrate satisfactory efficacy (effect size) to justify the cost associated with its implementation. If not, there may be uncertainty regarding how much of an improvement in nonadherence is necessary (i.e., the minimum effect size required) for the cost of the intervention to represent acceptable value.

A rigorous prior report has projected the cost-effectiveness of nonadherence interventions [3]. Unfortunately, this study may not always be applicable to the design of intervention trials for a number of reasons. First, it did not explicitly consider how reductions in nonadherence might increase medication expenditures, making nonadherence interventions seem more economically attractive than they really are. Second, minimum effect sizes were expressed exclusively in terms of short-term changes in viral load rather than in terms of changes in nonadherence. Nonadherence may have positive effects that are not mediated through short-term viral load changes (e.g., lessening the likelihood of drug resistance accrual) [4] and is increasingly feasible to measure with electronic medical records (EMRs) [5,6]. Finally, this study did not consider adherence interventions directed at risk factors for nonadherence that are particularly common in HIV populations (e.g., alcohol abuse, drug abuse, and psychiatric comorbidity) [7], and these risk factors may represent important intervention opportunities.

Because it is uncertain how much of an effect to require from adherence interventions in clinical trials, and it is uncertain when an adherence intervention merits incorporation into clinical practice, we have used a validated computer simulation of HIV infection [8] to estimate how much of a decrease in nonadherence would be required for an intervention to deliver acceptable value. In contrast to prior analyses, our analysis explicitly considers downstream costs from increased medication expenditures and interventions aimed at behavioral risk factors.

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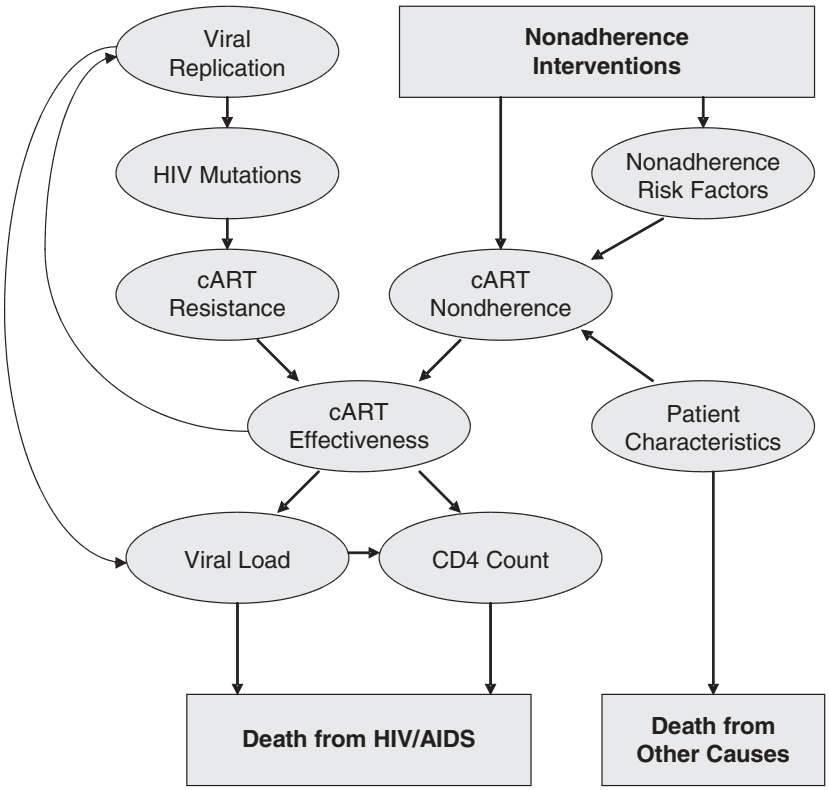

Figure 1 Schematic of computer simulation. The simulation is able to consider not only the shorter term impact of reducing combination antiretroviral therapy (ARV) nonadherence on improving viral load and CD4 count (particularly important for individuals with severe nonadherence), but also the longer term impact of reduced nonadherence on lowering ARV resistance accumulation (particularly important for individuals with moderate nonadherence).

Methods

We describe, first, our computer simulation of HIV progression; second, the types of nonadherence interventions that we use this simulation to evaluate; third, the target populations of these analyses; and fourth, our criterion for acceptable value and our analytical perspective.

Computer Simulation

We have developed a computer simulation of HIV progression that was developed "from the ground up" in the ARV era (Fig. 1). It differs from computer simulations used in prior simulations of nonadherence interventions [3] because it incorporates biologic processes that underlie the eventual decreased effectiveness of ARV (genotypic resistance accumulation and poor adherence). For this reason, it is not only able to estimate the short-term mortality impact of changes in ARV nonadherence because of improvements in viral load and CD4 count trajectories, but it is also able to estimate the long-term mortality impact of changes in ARV nonadherence because of improvements in drug resistance accrual risk. For example, it may be intuitively unclear whether increasing adherence from 50% to 62% would benefit a patient because an improvement in short-term outcomes from greater viral load suppression may be overshadowed by a worsening in long-term outcomes because of increased resistance accumulation. The simulation can weigh this trade-off explicitly, and can estimate whether this change in adherence would be favorable, together with the magnitude of its effect. Furthermore, the simulation is able to estimate the incremental costs that arise when more ARV doses are taken as a result of improving adherence.

The simulation can assign otherwise similar patient cohorts to different interventions and compare the impact of these interventions on designated outcomes. Because the simulation is probabilistic, it is able to represent much of the heterogeneity of actual patient populations (e.g., clinical events, such as deaths, may or may not happen within any particular time interval, and their probability of occurrence is based on known predictors). Its design is described in more detail elsewhere [8–10]. Its data inputs have not been changed from those used that are reported elsewhere because these resulted in the best calibration and validation of the model (Table 1). This model has closely reproduced Kaplan–Meier curves of time to treatment failure and survival among 3545 ARV-naive patients [8], has yielded 3-year mortality estimates similar to those from a 12,574 patient cohort that was distinct from the derivation cohort [8], and has replicated and explained clinically observed heterogeneity in the relationship of ARV adherence to resistance mutation accumulation [9,10].

Interventions

The advent of EMR systems makes it increasingly feasible to identify nonadherent patients during routine visits, and to screen them for risk factors. We reasoned that as health information technology becomes more sophisticated, patients may be increasingly targeted for nonadherence interventions if 1) they are thought to have suboptimal adherence based on validated algorithms that estimate adherence from pharmacy refill records, and/or 2) they have identifiable risk factors for nonadherence based on the results of common screening tests that are entered into the EMR system. Correspondingly, we analyzed two categories of hypothetical interventions; first, those that decreased the likelihood of antiretroviral nonadherence, and second, those that decreased the likelihood of behaviors that are known to be important modifiable risk factors for nonadherence (unhealthy alcohol use [incorporating hazardous alcohol consumption, as

Table 1 Inputs in computer simulation of HIV progression for patients on combination antiretroviral therapy (ARV). All were assumed to be 40 years old, have a pre-ARV CD4 count of 350 cells/ul, and have a pre-ARV viral load of 100,000 copies/ml

Parameter	Estimate(s)	Reference
Adherence impact on		
ARV viral load decrement	Increases linearly (0–2.9 log unit decrease as nonadherence increases from 0% to 100%)	[1,9]
ARV resistance accrual	Varies in U-shaped relationship (threefold increase then decrease as adherence increases from 0% to 100%)	[9]
Log viral load impact on		
ARV CD4 elevation	Increases linearly with log viral load decrement (70 cells/ul increase as log viral load decrement increases from 0 log units to 2.9 log units)	[9]
ARV resistance accrual	Increases nonlinearly (up to 30-fold increase as resistance develops to all ARV drugs)	[9]
HIV-related mortality	Increases nonlinearly (as much as from 0.09 to 0.18 as log viral load increases from <3.5 to >5.5)	[8]
CD4 impact on		
HIV-related mortality	Decreases nonlinearly (as much as from 0.18 to <0.01 as CD4 increases from <50 cells/ul to >500 cells/ul)	[8]
ARV resistance impact on		
ARV viral load decrement	Decreases linearly (2.9 log unit increase as proportion of resistant drugs in ARV regimen increases to 1)	[9]
Costs (yearly)		
ARV	$10,300	[3]
Non-ARV HIV care	Decreases nonlinearly with CD4 count (from $6400 with CD4 < 50 to $28,000 for CD4 > 200)	[11]
Utility		
Off-ARV utility	Increases nonlinearly with CD4 count (from 0.79 units with CD4 < 50 to 0.94 units for CD4 > 200	[12]
Utility decrement from ARV side effects	0.08 units	[13]
Proportion on ARV with side effects	67%	[13]
Behavioral risk factor impact on nonadherence (RR)		
Unhealthy alcohol use	RR 2.7	[7,14]
Drug dependence	RR 2.0	[7]
Depression	RR 1.7	[7]

RR, relative risk.

well as harmful alcohol use, alcohol abuse, and alcohol dependence] [15], drug dependence, and depression). Addressing these risk factors may be a complementary strategy to addressing nonadherence itself because clinical data suggest that the impact on antiretroviral nonadherence is greatest for unhealthy alcohol use (relative risk [RR] for nonadherence: 2.7 for "heavy frequent alcohol use" [7] as well as for hazardous alcohol use [14]) and somewhat lower for drug abuse (RR for nonadherence: 1.6–2.3, depending upon drug type) or depression (RR for nonadherence: 1.7).

We chose RR as an intervention outcome metric because it was applicable across a wide range of targeted behaviors and risk factors (i.e., nonadherence, as well as risk factors for nonadherence), and because it scales well with different levels of baseline nonadherence. For RRs between 0 and 1, larger RRs correspond to lesser effects, whereas smaller RRs correspond to greater effects. In addition, we report outcomes using the alternate metric of absolute risk reduction (ARR). In contrast to RRs, larger ARRs correspond to greater effects, whereas smaller ARRs correspond to lesser effects. Note that ARR does not scale with baseline nonadherence, and therefore, the maximum ARR is dependent upon the baseline nonadherence (e.g., if baseline nonadherence is 0.20, then the maximum ARR is 0.20).

To work through an illustrative example, for patients with a baseline nonadherence of 0.20, an intervention with an ARR of 0.20 would lower the proportion of nonadherence from 0.20 to 0, which would correspond to an RR of 0. For patients with 0.50 nonadherence at baseline, an intervention with an ARR of 0.20 would lower the proportion of nonadherence from 0.50 to 0.30, corresponding to an RR of 0.6. Because alcohol increases the RR of nonadherence by 2.7, an alcohol intervention that was completely effective would lower the proportion of nonadherence from its baseline value to that baseline value divided by 2.7. Analogous calculations apply to drug use and depression interventions.

Interventions may have variable frequencies and durations, ranging from one-time events such as a brief motivational intervention to recurrent interventions such as a directly observed therapy. For this reason, we analyzed alternate scenarios regarding intervention frequencies and duration of effect: 1) an intervention that had a one-time cost and a short-term effect (6 months, i.e., a typical follow-up period in a clinical trial), and 2) an intervention that had a recurrent, yearly cost and an enduring effect. In sensitivity analyses, we analyzed the most optimistic scenario in which an intervention had a one-time cost but had a persistent effect.

Target Population

We considered adherence interventions for patients with HIV infection who are already prescribed ARV and who are known to have adherence difficulties (e.g., pharmacy refill records suggesting that adherence is suboptimal). We specified two separate populations who may be targeted for adherence interventions: persons with moderate nonadherence (defined as not taking 20% of prescribed ARV doses as directed) and persons with severe nonadherence (defined as not taking 50% of prescribed ARV doses as directed). Patients with moderate nonadherence may be suitable targets for adherence improvement because they are at particularly high risk of developing resistance mutations because the inverse U-shaped relationship between adherence and resistance accumulation peaks around this level [4,9], and because higher adherence may be required to maximize viral load suppression [16,17]. Patients with severe nonadherence may be suit-

able targets for adherence improvement because they have poorer viral load and CD4 responses to ARV [1,18], which increases the risk of AIDS and HIV-related death.

All patients in our target population had CD4 counts of 350 cells/ul, pre-ARV viral loads and 100,000/mL, and ages of 40 years because these are similar to the pre-ARV-initiation characteristics of multiple clinical cohorts, and facilitate comparisons with our previous analyses; however, we varied these characteristics in sensitivity analyses.

Criterion for Acceptable Value

Published reports suggest that individuals in the United States are willing to pay $100,000 to obtain an additional life-year or quality-adjusted life-year of benefit from medical care, and correspondingly, that $100,000 per life-year or per quality-adjusted life-year may be thought of as a lower bound for acceptable value [19]. Accordingly, in our base case, we used our computer simulation to estimate the smallest intervention effect size that delivered 1 life-year per $100,000 spent, and therefore, was consistent with acceptable value. In sensitivity analyses, we used the simulation to estimate the smallest intervention effect size that delivered 1 quality-adjusted life-year per $100,000 spent.

Analytical Perspective

We inflated all costs to $2003 using the consumer price index for all goods and services [20]. We used a societal perspective for our analysis as recommended by the Panel on Cost-Effectiveness in Health Care [21], meaning that we treated costs identically regardless of whether they were incurred by payers or patients, or whether they accrued from inpatient expenses, outpatient expenses, or drugs. Also, as recommended by the Panel on Cost-Effectiveness in Health Care, we used a discount rate of 3%. A discount rate reflects the idea that costs and benefits that accrue in the future are valued less than costs and benefits that accrue today, even after adjusting for inflation. We followed all patients until death from HIV-related or non-HIV-related causes, and therefore assumed an indefinite time horizon. Each cohort simulation was run with 1,000,000 hypothetical patients.

Results

We used the computer simulation to estimate the impact of hypothetical nonadherence interventions on life expectancy and costs. By comparing the increase in life expectancy with the increase in costs (from the intervention itself, as well as from the downstream costs of the intervention such as increased medication costs), we were able to estimate the incremental cost-effectiveness of the nonadherence intervention. Consequently, we were able to estimate the minimum effect size necessary for an intervention to offer acceptable value at a particular cost.

We first describe our results analyzing the value of interventions directly acting on nonadherence, followed by our results analyzing the value of interventions acting on particularly important risk factors for nonadherence (unhealthy alcohol use, drug dependence, and depression).

Nonadherence Interventions

A one-time nonadherence intervention costing $1000 could offer favorable value with a relatively small effect size of RR $\leq$ 0.82 (ARR $\geq$ 0.04) for 20% baseline nonadherence and RR $\leq$ 0.90 (ARR $\geq$ 0.05) for 50% baseline nonadherence. As the adherence intervention became more expensive, however, it was less likely to offer a favorable value (Fig. 2). Even when the nonadherence intervention was assumed to be completely effective, it could not offer favorable value if it costs more than $4500 for patients with 20% baseline nonadherence, or if it costs more than $6500 for patients with 50% baseline nonadherence.

When nonadherence interventions were assumed to have sustained costs and effects (Table 2), smaller effect sizes were compatible with acceptable value. A sustained nonadherence intervention costing $1000 annually could offer a favorable value with effect sizes of RR $\leq$ 0.87 (ARR $\geq$ 0.03) for patients with 20% baseline nonadherence and effect sizes of RR $\leq$ 0.95 (ARR $\geq$ 0.03) for patients with 50% baseline nonadherence. As the sustained adherence intervention became more expensive, it was less likely to offer favorable value. Even when the sustained nonadherence intervention was assumed to have complete, enduring effectiveness, it could not offer favorable value if it costs more than $7000 annually for patients with 20% baseline nonadherence, or if it costs more than approximately $13,000 for patients wth 50% baseline nonadherence.

The minimum effect size did not vary linearly with intervention costs because a substantial portion of the incremental costs of the nonadherence intervention did not arise from the intrinsic cost of the intervention, but rather arose from increased antiretroviral expenditures, particularly for intervention costs below $10,000 (Fig. 3).

Risk Factor Interventions

For nonadherent patients who screen positive for unhealthy alcohol consumption, a one-time unhealthy alcohol use intervention costing $1000 could offer favorable value with a moderate effect size of RR $\leq$ 0.74 (ARR $\geq$ 0.26) for unhealthy alcohol use persisting, with 50% baseline nonadherence. As the alcohol intervention became more expensive, however, it was less likely to offer favorable value (Table 3). Even when the alcohol intervention was assumed to be completely effective, it could not offer favorable value if it costs more than $4300 for patients with 50% baseline nonadherence. Results for continuous rather than one-time interventions showed that somewhat higher costs were compatible with acceptable value (for example, $6400 vs. $4300 for a completely effective alcohol intervention, continuous vs. one time). Results for patients with lower baseline nonadherence (20% rather than 50%) suggested that lower costs are required for acceptable value (for example, $3600 vs. $4300 for a completely effective alcohol intervention, 20% vs. 50% baseline nonadherence).

Results for drug abuse and depression interventions in nonadherent patients who screen positive were generally similar to results for alcohol interventions, except that achieving the acceptable value required larger effect sizes (Tables 4 and 5). A one-time drug abuse intervention costing $1000 required a substantial effect size to offer favorable value (RR $\leq$ 0.59 [ARR $\geq$ 0.41] with 50% baseline nonadherence). Even when the drug abuse intervention was assumed to be completely effective, it could not offer favorable value if it costs more than $3100 for patients with 50% baseline nonadherence. Results for depression interventions differed little from results for drug abuse interventions, in accordance with the similar assumptions regarding their impact on nonadherence that were used as inputs to the model.

Sensitivity Analyses

Our results varied greatly with the presumed duration of effect of the nonadherence interventions. When we assumed that the effect of an adherence intervention persisted beyond its duration, small effect sizes (RR $\leq$ 0.91 [ARR $\geq$ 0.02] for adherence

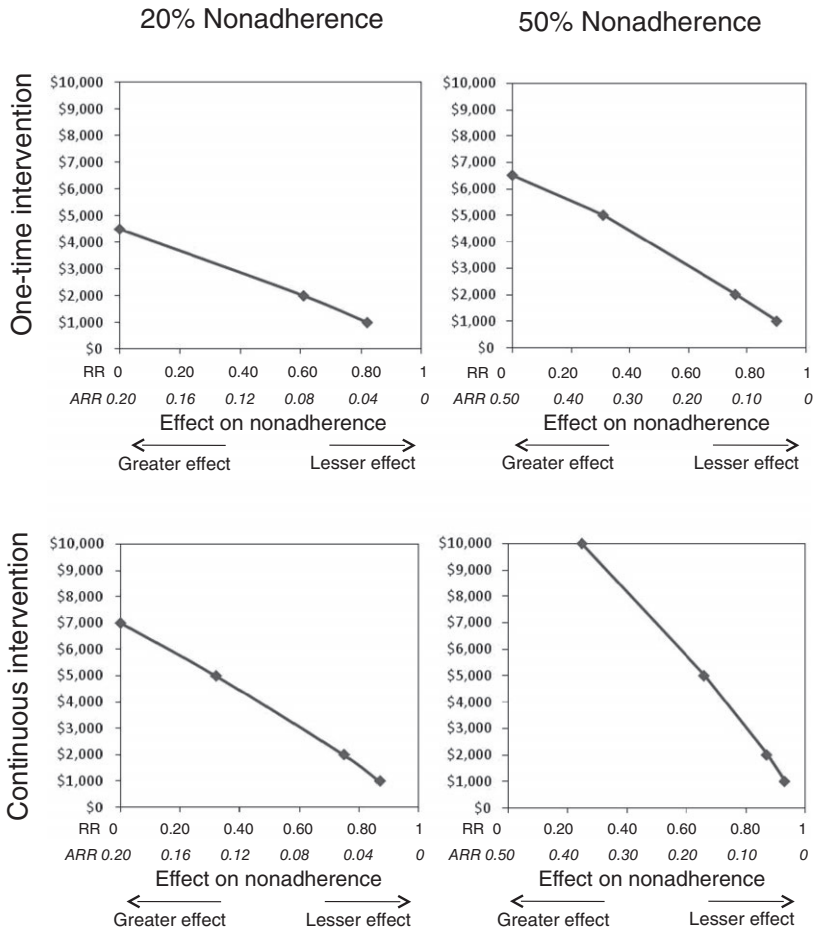

Figure 2 Adherence intervention effects and costs compatible with acceptable value (≤$100,000/quality-adjusted life-year), stratified by baseline nonadherence and persistence of the intervention. Interventions aimed at severely nonadherent patients (50% doses taken as directed) generally confer higher value than interventions aimed at moderately adherent patients (20% taken as directed), even though improving the adherence of severely nonadherent patients may lead to more rapid accumulation of resistance mutations. ARR, absolute risk reduction; RR, relative risk.

Table 2 Effect sizes required for nonadherence interventions to have acceptable value,* by baseline nonadherence and intervention cost. An intervention is assumed to impact the relative risk (RR) of nonadherence. An RR reduction of 1 means nonadherence is unchanged, and an RR of 0 means nonadherence is eliminated

Baseline nonadherence (% doses)	Duration of intervention	Cost of intervention ($)†	Smallest effect with acceptable value (largest RR)
20%	One time	1,000	0.82
		2,000	0.61
		5,000	None
		10,000	None
	Persistent	1,000	0.87
		2,000	0.75
		5,000	0.32
		10,000	None
50%	One time	1,000	0.90
		2,000	0.76
		5,000	0.31
		10,000	None
	Persistent	1,000	0.93
		2,000	0.87
		5,000	0.66
		10,000	0.25

*Acceptable value defined as ≤$100,000 per life-year.
†If intervention is recurrent, cost is yearly.

interventions; RR ≤ 0.77 [ARR ≥ 0.05] for risk factor interventions) delivered acceptable value even for expensive interventions (one-time cost of $10,000).

Discussion

Our results suggest that nonadherence interventions with small effects (e.g., RR as high as 0.95 or ARR as small as 0.03) could represent acceptable value if they cost approximately $1000 per year or less (i.e., the approximate cost of alarms or automated medication dispensers) [3]. Interventions with larger effects (RR less than 0.50 or ARR greater than 0.10) could often represent acceptable value if they cost approximately $5000 per year or less. For example, because directly observed therapy is likely to reduce nonadherence by an ARR of at least 0.12 in injection drug-using populations [22] and its approximate annual cost is $5000 (for 5 days per week directly observed therapy with one contact daily [3]), it has the potential to offer favorable value. As intervention costs approach $10,000 per year (i.e., the approximate cost of 7 days per week directly observed therapy, or directly observed therapy with two contacts daily), effects would need to be implausibly large to represent acceptable value. It is important to note that directly observed therapies [22–24], voucher reinforcements [25], and behavioral interventions are potential candidates for delivering acceptable value.

Adherence interventions could have a substantial value regardless of whether they were aimed at patients with moderate nonadherence (20% of doses not taken as directed) or severe

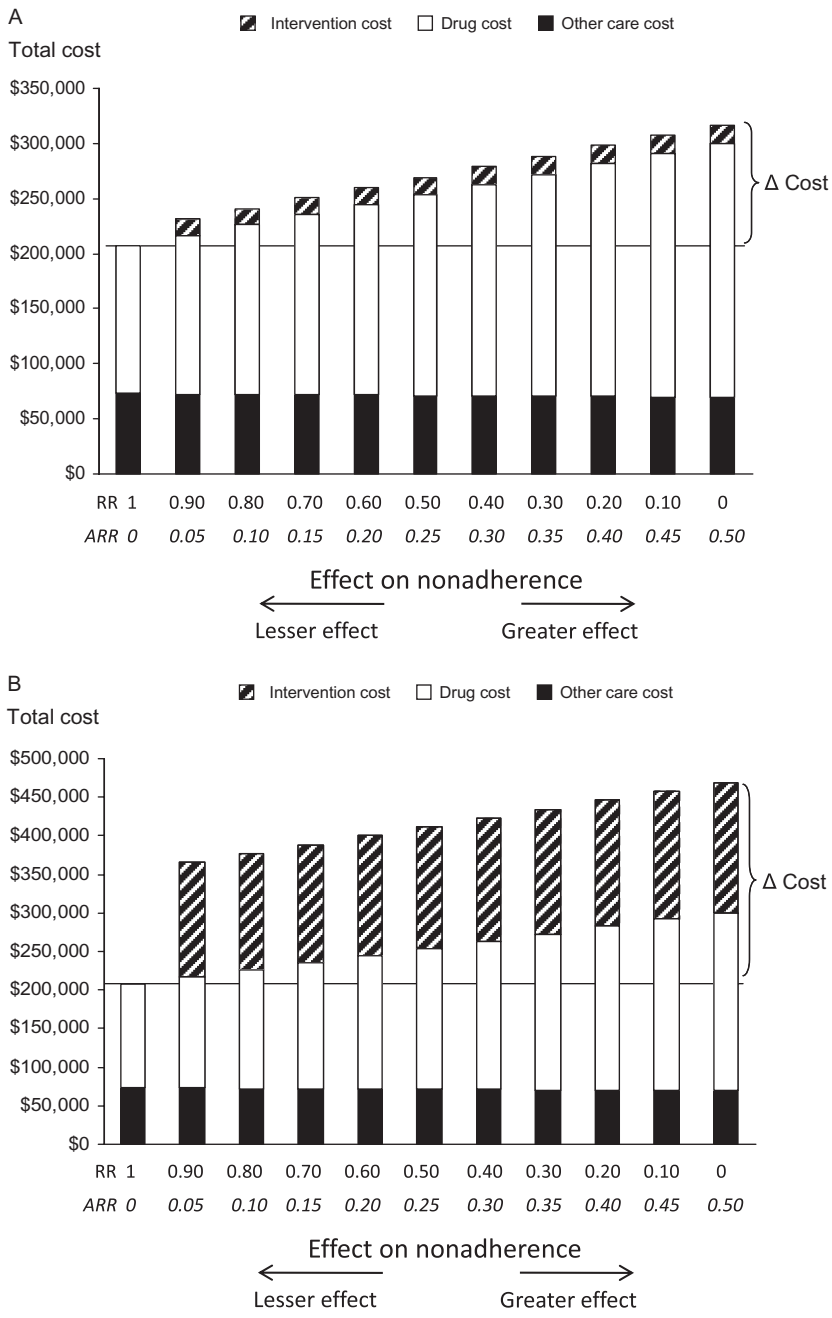

Figure 3 Proportional contributions of adherence intervention costs, combination antiretroviral therapy drug costs, and other costs to overall HIV expenditures. Adherence interventions increase expenditures not only because of the costs of the interventions themselves, but also because of increased drug costs, particularly if the interventions are more effective (and therefore result in more drug doses being consumed). The proportional contribution of the nonadherence intervention remains small if its cost is $1000 per year (A). For this reason, its value would rise little even if its costs were reduced further. In contrast, the proportional contribution of a nonadherence intervention is large if its cost is $10,000 per year (B). For this reason, its value would rise substantially if its costs were reduced further.

nonadherence (50% of doses not taken as directed). Nevertheless, the minimum effect required varied, depending upon which outcome metric was chosen. Using the metric of RR, patients with severe nonadherence could obtain a favorable value with interventions that had substantially smaller effects compared with patients with moderate nonadherence, whereas using the metric of ARR, patients with severe nonadherence could only obtain a favorable value with interventions that had slightly larger effects compared with patients with moderate nonadherence. The substantial value of nonadherence interventions for patients with moderate nonadherence may have great implications for HIV care because many patients in care have nonadherence in this range [1].

Our results underscore the potential benefit for interventions aimed at nonadherence risk factors (unhealthy alcohol use, drug dependence, and depression), if these risk factors are indeed causally related to nonadherence. For example, an intervention to reduce unhealthy alcohol use that costs up to $2000 per year may deliver acceptable value if it reduces unhealthy alcohol use by RR $\leq$ 0.56 (ARR $\geq$ 0.44) for moderately nonadherent individuals and by RR $\leq$ 0.71 (ARR $\geq$ 0.29) for severely nonadherent individuals (e.g., topiramate reduces heavy drinking days by RR $\leq$ 0.48 compared with placebo and may fulfill these criteria [26]). An intervention to reduce depression that costs up to $2000 per year may deliver acceptable value if it reduces depression by RR $\leq$ 0.30 (ARR $\geq$ 0.70) for moderately nonadherent

Table 3 Effect sizes required for unhealthy alcohol use interventions to have acceptable value,* by baseline nonadherence level and intervention cost. An intervention is assumed to impact the relative risk (RR) of unhealthy alcohol use. An RR reduction of 1 means unhealthy alcohol use is unchanged, and an RR of 0 means unhealthy alcohol use is eliminated

Baseline nonadherence (% doses)	Time course of intervention	Cost of intervention ($)†	Smallest effect with acceptable value (largest RR)‡
20%	One time	1,000	0.73
		2,000	0.42
		5,000	None
		10,000	None
	Persistent	1,000	0.78
		2,000	0.56
		5,000	None
		10,000	None
50%	One time	1,000	0.74
		2,000	0.53
		5,000	None
		10,000	None
	Persistent	1,000	0.86
		2,000	0.71
		5,000	0.25
		10,000	None

*Acceptable value defined as ≤$100,000 per life-year.
†If intervention is recurrent, cost is yearly.
‡Interventions with very small effect sizes (RR between 0.95 and 1) could not be evaluated with certainty.

Table 4 Effect sizes required for drug dependence interventions to have acceptable value,* by baseline nonadherence level and intervention cost. An intervention is assumed to impact the relative risk (RR) of drug dependence. An RR reduction of 1 means drug dependence is unchanged, and an RR of 0 means drug dependence is eliminated

Baseline nonadherence (% doses)	Time course of intervention	Cost of intervention ($)†	Smallest effect with acceptable value (largest RR)‡
20%	One time	1,000	0.72
		2,000	0.35
		5,000	None
		10,000	None
	Continuous	1,000	0.72
		2,000	0.42
		5,000	None
		10,000	None
50%	One time	1,000	0.59
		2,000	0.33
		5,000	None
		10,000	None
	Continuous	1,000	0.80
		2,000	0.59
		5,000	None
		10,000	None

*Acceptable value defined as ≤$100,000 per life-year.
†If intervention is recurrent, cost is yearly.
‡Interventions with very small effect sizes (RR between 0.95 and 1) could not be evaluated with certainty.

individuals and by RR ≤ 0.47 (ARR ≥ 0.53) for severely nonadherent individuals.

Our results were somewhat more pessimistic than the results of Goldie et al. [3], who estimated that nonadherence interventions costing as much as $12,000 per year may represent acceptable value. In contrast, we found that interventions costing $5000 per year or more were unlikely to represent acceptable value, unless they had one-time costs and their effects persisted indefinitely. The main reason why our results are more pessimistic is because we consider the increase in downstream costs that result from increasing adherence. Patients who start to adhere more use greater amounts of antiretroviral medications, and these medications are often expensive, sometimes contributing more to the incremental cost burden than the intervention itself.

Our study has notable limitations. We assumed that risk behaviors only impact mortality through adherence, whereas they may impact mortality in other ways (e.g., an effective intervention for alcohol may reduce cirrhosis deaths, whereas an effective intervention for drug dependence may reduce overdose deaths). In our analyses, we assumed that behavioral risk factors impacted life expectancy solely through their impact on antiretroviral adherence, and not through other health effects. We assumed causal relationships between nonadherence and behavioral risk factors, whereas the associations are based on observational studies that cannot demonstrate causality. The poorest adherers often miss clinic visits and, therefore, are difficult to target with the types of interventions that we studied. Some of our cost estimates date from the early era of highly active combination ARV [3,11], yet their age is unlikely to undermine our analysis because they reflect the current landscape of HIV costs (e.g., reduced inpatient costs and increased drug costs) and because ARV costs in the United States have changed relatively little in real terms [27]. We assumed a willingness to pay for health benefits based on the society at large because data specific to our particular populations (HIV and substance abuse) are inadequate. Finally, our results may not apply to results from pilot interventions, which often have high "start-up" costs that could be amortized over longer time periods.

In conclusion, nonadherence interventions may represent some of the "lowest hanging fruit" for improving HIV care and have the advantage of not requiring any incremental technological or scientific advances. Indeed, the promulgation of health information technology and EMRs may have the collateral effect of making it easier to identify patients with adherence problems and to measure the success of interventions to help them. Our results may inform the design of clinical trials of adherence interventions because estimations of minimum acceptable effect

Table 5 Effect sizes required for depression interventions to have acceptable value,* by baseline nonadherence level and intervention cost. An intervention is assumed to impact the relative risk (RR) of depression. An RR reduction of 1 means depression is unchanged, and an RR of 0 means depression is eliminated

Baseline nonadherence (% doses)	Time course of intervention	Cost of intervention ($)†	Smallest effect with acceptable value (largest RR)‡
20%	One time	1,000	0.52
		2,000	0.16
		5,000	None
		10,000	None
	Continuous	1,000	0.65
		2,000	0.30
		5,000	None
		10,000	None
50%	One time	1,000	0.69
		2,000	0.36
		5,000	None
		10,000	None
	Continuous	1,000	0.73
		2,000	0.47
		5,000	None
		10,000	None

*Acceptable value defined as ≤$100,000 per life-year.
†If intervention is recurrent, cost is yearly.
‡Interventions with very small effect sizes (RR between 0.95 and 1) could not be evaluated with certainty.

size may inform hypothesis specification and statistical power requirements. In addition, our results may inform resource allocation decisions of organizations seeking to maximize quality of care.

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